1,023,720

# PATENT SPECIFICATION

NO DRAWINGS

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**Int. Cl.:**—C 07 d

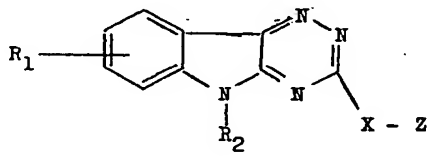
## COMPLETE SPECIFICATION

# as-Triazino (5,6-b) Indoles

We, ALLEN & HANBURYS LIMITED, of Three Colts Lane, Bethnal Green, London, E.2, England, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel heterocyclic compounds having therapeutic activity, for example anti-viral activity.

The present invention provides *as*-triazino-(5,6-b)indoles of the general formula



(I)

wherein $R_1$ is a hydrogen or halogen atom or an alkyl, aralkyl, hydroxy, alkoxy, nitro, amino or trifluoromethyl radical, $R_2$ is a hydrogen atom or an alkyl or aralkyl radical, X is an oxygen atom, a sulphur atom or a SO, $SO_2$ or $NR_3$ radical where $R_3$ is a hydrogen atom or a methyl radical, Z is an alkyl, alkenyl, aryl or aralkyl radical or a radical of the general formula —AlkOH or —$AlkNR_4R_5$, where Alk is a branched or straight chain alkylene radical containing 2 to 10 carbon atoms and $R_4$ and $R_5$ are hydrogen atoms or alkyl radicals or together with the adjacent nitrogen atom form a heterocyclic ring which may contain additional hetero atoms or Z is a hydrogen atom when X is an oxygen or sulphur atom or Z is an amino group when X is a NH radical, or X—Z together form a N-containing saturated heterocyclic ring linked through the ring nitrogen atoms, or X—Z together represent a hydrogen atom, and pharmaceutically acceptable salts thereof.

Most of the compounds of formula I are bases and form acid addition and quaternary ammonium salts. However, some compounds of formula I, e.g. the 3-mercapto- and 3-hydroxy-*as*-trizino(5,6-b)indoles, are weak acids and form stable alkali salts. All types of pharmaceutically acceptable salts are included within the scope of the invention.

The compounds of the present invention have been found to have useful biological activity. Some of the compounds have been found to possess antiviral activity, whilst others for example possess antibacterial activity. The compounds may be employed in the usual forms for therapeutic administration. For example, they may be formulated with a pharmaceutical carrier to provide tablets, capsules, suppositories, injection solutions and the like.

The preferred compounds of the invention are 3 - mercapto - 5 - methyl - 8 - nitro - *as*-triazino(5,6 - b)indole, 3 - (β - N - morpholino - ethyl) - mercapto - 5 - methyl - *as*-triazino(5,6 - b)indole, 3 - (2 - dimethylaminoethylmercapto) - 5 - methyl - *as* - triazino(5,6 - b)indole, 3 - methylmercapto - 5 - propyl - *as* - triazino(5,6 - b)indole and 3-(3 - hydroxypropylamino) - 5 - methyl - *as*-triazino(5,6 - b)indole and their pharmaceutically acceptable salts.

Our method of testing the compounds is as follows:

Each dose of a sample is added to 8 tubes of confluent cells; 16 hours later a 100 $TCD_{50}$

(5,6-b)indole of formula III with an aminating agent or hydrazine.

The aminating agent may be, for example, a primary amine (such as alkylamine, a hydroxyalkylamine or an aminoalkylamine)-dimethylamine or a heterocyclic amine such as morpholine or piperidine. The compound of formula III may be heated, for example, under reflux, with the aminating agent in an indifferent solvent such as butanol or an excess of the reacting amine may be used as the solvent. Alternatively, if the aminating agent is a low boiling amine, an alcoholic solution of it may be heated in a sealed tube with the compound of formula III.

The reaction of a compound of formula III with hydrazine yields a 3-hydrazino-*as*-triazino-(5,6-b)indole. The mercapto compound may, for example, be heated with hydrazine hydrate.

Compounds in which X—Z together represent a hydrogen atom may be prepared by treating 3-hydrazino-*as*-triazino(5,6-b)indoles with oxidising agents such as yellow mercuric oxide.

c) Preparation of compounds of formula I in which X is an oxygen atom.

3-Hydroxy-*as*-triazino(5,6-b)indoles may be prepared by known methods for converting mercapto groups to hydroxy groups. For example, 3-mercapto-*as*-triazino(5,6-b)indoles of formula III may be reacted with hydrogen peroxide or chloroacetic acid. Ethers of 3-hydroxy-*as*-triazino(5,6-b)indoles may be prepared by methods known in the art.

If desired, the basic compounds of formula I obtained by any of the processes given above may be quaternised or converted into their salts with inorganic or organic acids and the acidic compounds of formula I may be converted into their salts with bases.

The following examples illustrate the invention:

EXAMPLE 1.

Preparation of 3-mercapto-5-methyl-*as*-triazino(5,6-b)indole.

(i) 6.0 G. of N-methylisatin thiosemicarbazone was suspended in 1.5 litres of water containing 15 ml. of ammonia solution (s.g. 0.880) and the mixture was boiled under reflux for 24 hours. After cooling the solution somewhat, a small amount of insoluble material was removed by filtration and rejected. The filtrate was evaporated under reduced pressure to about one third of its volume and, after cooling, the yellow solid which separated was removed by filtration and recrystallised from 50% aqueous dimethyl formamide to give 3-mercapto - 5 - methyl - *as* - triazino(5,6-b)-indole, m.p. 279—281°C.

The following compounds were prepared in a similar manner:

3 - mercapto - *as* - triazino(5,6 - b)indole, m.p. higher than 360°C.

3 - mercapto - 5 - ethyl - *as* - triazino-(5,6 - b)indole, m.p. 294°C.

3 - mercapto - 5 - propyl - *as* - triazino-(5,6 - b)indole, m.p. 278°C.

(ii) 5 G. of N-methylisatin thiosemicarbazone was suspended in 100 ml. of water containing 4.4 g. of potassium carbonate and the mixture was boiled under reflux for 75 minutes. The orange coloured solution was cooled, diluted with 100 ml. of water and acidified with acetic acid. The yellow solid which separated was removed by filtration, washed with water, dried at 100°C. and recrystallised from a large volume of methanol to give 3 - mercapto - 5 - methyl - *as* - triazino-(5,6-b)indole, m.p. 278 to 282°C.

The following compounds were prepared in a similar manner:

3 - mercapto - *as* - triazino(5,6 - b)indole, m.p. higher than 360°C.

3 - mercapto - 5 - methyl - 8 - chloro - *as*-triazino(5,6 - b)indole, m.p. 315 to 316°C.

3 - mercapto - 8 - nitro - *as* - triazino-(5,6 - b)indole, m.p. higher than 350°C.

3 - mercapto - 8 - methoxy - *as* - triazino-(5,6 - b)indole, m.p. 331°C.

3 - mercapto - 5 - methyl - 8 - bromo - *as*-triazino(5,6 - b)indole, m.p. higher than 350°C.

3 - mercapto - 5 - methyl - 8 - nitro - *as*-triazino(5,6 - b)indole, m.p. 283°C.

(iii) 16 G. of N-methylisatin, 10 g. of thiosemicarbazide and 21 g. of potassium carbonate were boiled under reflux in 500 ml. of water for 7 hours. A small amount of insoluble material was removed by filtration and rejected and the filtrate was cooled and acidified with acetic acid. The solid which separated was removed by filtration, washed with water and dried at 100°C. to give 3-mercapto - 5 - methyl - *as* - triazino(5,6 - b)-indole, m.p. 275 to 281°C.

The following compounds were prepared in a similar manner:

3 - mercapto - 7 - methoxy - *as* - triazino-(5,6 - b)indole, m.p. 309°C.

3 - mercapto - 5 - propyl - 8 - chloro - *as*-triazino(5,6 - b)indole, m.p. 270 to 275°C.

EXAMPLE 2.

Preparation of 3-hydrazino-5-methyl-*as*-triazino(5,6-b)indole.

2.75 G. of 3 - mercapto - 5 - methyl - *as*-triazino(5,6-b)indole was boiled under reflux for 30 minutes in 20 ml. of hydrazine hydrate. The mercapto compound rapidly dissolved giving a red solution which soon commenced to deposit yellow needles. The mixture was cooled, the product removed by filtration and recrystallized from ethanol to give 3-hydrazino-5 - methyl - *as* - triazino(5,6-b)indole, m.p. 221 to 223° C.

EXAMPLE 3.

Preparation of 3 - (β - N - morpholino - ethyl)-mercapto - 5 - methyl - *as* - triazino-(5,6 - b)indole.

10.8 G. of 3 - mercapto - 5 - methyl - *as*-triazino(5,6 - b)indole was dissolved in 120

for 8 hours. During this time the solid dissolved and hydrogen sulphide was evolved. On cooling the reaction mixture, a yellow solid separated. The mixture was diluted with about 200 ml. of water and the solid, removed by filtration, was recrystallised from 50% aqueous ethanol. The product was obtained as pale yellow needles, m.p. 235 to 236°C.

EXAMPLE 10.

Preparation of 3-(3-hydroxypropylamino)-5-methyl-*as*-triazino(5,6-b)indole.

A solution of 2 g. of 3-mercapto-5-methyl-*as*-triazino(5,6-b)indole and 20 ml. of 3-aminopropanol was refluxed for 1.5 hours, hydrogen sulphide being evolved. On cooling, the solution was poured into water and the precipitated solid was removed by filtration, washed with water and dried. Recrystallisation from ethanol gave 3-(3-hydroxypropylamino)-5-methyl-*as*-triazino(5,6-b)indole as yellow needles, m.p. 164 to 165°C.

The hydrochloride crystallised from ethanol as yellow needles, m.p. 214 to 215°C.

The following compounds were prepared in a similar manner:

3 - (2 - hydroxyethylamino) - *as* - triazino-(5,6-b)indole, m.p. 270 to 271°C.

3 - (3 - hydroxypropylamino) - *as* - triazino-(5,6-b)indole, m.p. 248 to 249°C.

8 - chloro - 3 - (2 - hydroxyethylamino)-5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 262 to 263°C.

8 - chloro - 3 - (3 - hydroxypropylamino)-5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 203 to 204°C.

EXAMPLE 11.

Preparation of 3-(5-hydroxypentylamino)-5-methyl-*as*-triazino(5,6-b)indole.

A solution of 2 g. of 3-mercapto-5-methyl-*as*-triazino(5,6-b)indole in 10 g. of 5-aminopentanol was heated at 140—160°C. (internal temperature) for 30 minutes, hydrogen sulphide being evolved. On cooling the solution was poured into water and the precipitated solid was removed by filtration, washed with water and dried. Recrystallisation from ethanol gave 3 - (5 - hydroxypentylamino) - 5 - methyl-*as* - triazino(5,6 - b)indole as yellow needles, m.p. 158 to 158.5°C.

The hydrochloride crystallised from ethanol as yellow needles, m.p. 191 to 192°C.

The following compound was obtained in a similar manner:

3 - (6 - hydroxyhexylamino) - 5 - methyl-*as* - triazino(5,6 - b)indole, m.p. 124 to 125°C.

EXAMPLE 12.

Preparation of 3-dodecylamino-5-methyl-*as*-triazino(5,6-b)indole.

1 G. of 3 - mercapto - 5 - methyl - *as*-triazino(5,6 - b)indole and 4 g. of *n*-dodecylamine were heated together at 130°C. for 8 hours. On cooling the mixture a solid separated. Ether was added and the solid was removed by filtration and recrystallised from ethyl acetate giving the required amine, m.p. 119 to 120°C.

EXAMPLE 13.

Preparation of 3-benzylamino-5-methyl-*as*-triazino(5,6-b)indole

4.3 G. of 3 - mercapto - 5 - methyl - *as*-triazino(5,6 - b)indole and 1·1 ml. of benzylamine were heated together at 130°C. for 8 hours. On cooling the mixture crystals separated and, after the addition of methanol, were removed by filtration. Recrystallisation from ethanol gave colourless hexagonal plates, m.p. 224°C.

The following compounds were prepared in a similar manner:

3 - hexylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 162 to 163°C.

3 - heptylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 136°C.

3 - octylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 131°C.

3 - decylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 125°C.

3 - hexadecylamino - 5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 112°C.

3 - octadecylamino - 5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 99°C.

3 - (2 - phenethylamino) - 5 - methyl - *as*-triazino(5,6 - b)indole, m.p. 186°C.

EXAMPLE 14.

Preparation of 3-dimethylamino-*as*-triazino(5,6-b)indole.

1 G. of 3 - mercapto - *as* - triazino(5,6 - b)-indole and 20 ml. of a 33% solution of dimethylamine in ethanol were heated in a sealed tube at about 150°C. for 8 hours. After cooling, the tube was opened and the yellow crystals which had separated were removed by filtration and recrystallised by extraction with ethanol in a Soxhlet extractor. The product was obtained as pale yellow plates, m.p. 342 to 346°C.

The following compounds were prepared in a similar manner:

3 - dimethylamino - 5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 170°C.

3 - methylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 250°C.

3 - ethylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 213°C.

3 - propylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 189°C.

3 - *iso*propylamino - 5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 198°C.

3 - butylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole, m.p. 165°C.

3 - *n* - amylamino - 5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 168°C.

3 - *iso* - amylamino - 5 - methyl - *as* - triazino(5,6 - b)indole, m.p. 187°C.

3 - N - piperidyl - 5 - methyl - as - *tri*-azino(5,6 - b)indole, m.p. 180°C.

EXAMPLE 24.

Preparation of 3-ethylamino-5-methyl-*as*-triazino(5,6-b)indole hydrochloride.

1 G. of 3 - ethylamino - 5 - methyl - *as*-triazino(5,6 - b)indole was dissolved in 20 ml. of an 8% solution of hydrogen chloride in methanol. On the addition of 200 ml. of ether, the hydrochloride separated as yellow microcrystals, which after drying in vacuo, melted at 262°C.

The following compounds were prepared in a similar manner:

3 - ($2^1$ - phenylethylamino) - 5 - methyl-*as* - triazino(5,6 - b)indole hydrochloride, m.p. 220°C.

3 - benzylamino - 5 - methyl - *as* - triazino-(5,6 - b)indole hydrochloride, m.p. 213°C.

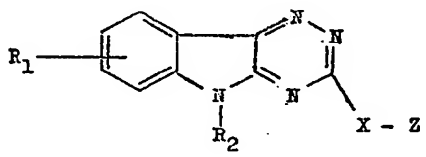
3 - N - piperidyl - 5 - methyl - *as* -triazino-(5,6 - b)indole hydrochloride, m.p. 222°C.

3 - N - morpholinyl - 5 - methyl - *as* - triazino(5,6 - b)indole hydrochloride, m.p. 234°C.

3 - dimethylamino - 5 - methyl - *as* - triazino(5,6 - b)indole hydrochloride, m.p. 256°C.

WHAT WE CLAIM IS:—

1. *as*-Triazino(5,6-b)indoles of the general formula




(I)

where $R_1$ is a hydrogen or halogen atom or an alkyl, aralkyl, hydroxy, alkoxy, nitro, amino or trifluoromethyl radical, $R_2$ is a hydrogen atom or an alkyl or aralkyl radical, X is an oxygen atom, a sulphur atom or a SO, $SO_2$ or $NR_3$ radical where $R_3$ is a hydrogen atom or a methyl radical, Z is an alkyl, alkenyl, aryl or aralkyl radical or a radical of the general formula —AlkOH or —$AlkNR_4R_5$, where Alk is a branched or straight chain alkylene radical containing 2 to 10 carbon atoms and $R_4$ and $R_5$ are hydrogen atoms or alkyl radicals or together with the adjacent nitrogen atom form a heterocyclic ring which may contain additional hetero atoms or Z is a hydrogen atom when X is an oxygen or sulphur atom or Z is an amino group when X is a NH radical, or X—Z together form a N-containing saturated heterocyclic ring linked through the ring nitrogen atom or X—Z together represent a hydrogen atom and pharmaceutically acceptable salts thereof.

2. 3 - Mercapto - 5 - methyl - *as* - triazino-(5,6 - b)indole.

3. 3 - Mercapto - *as* - triazino(5,6 - b)-indole.

4. 3 - Mercapto 5 - ethyl - *as* - triazino-(5,6 - b)indole.

5. 3 - Mercapto - 5 - propyl - *as* - triazino-(5,6 - b)indole.

6. 3 - Mercapto - 5 - methyl - 8 - chloro-*as* - triazino(5,6 - b)indole.

7. 3 - Mercapto - 8 - nitro - *as* - triazino-(5,6 - b)indole.

8. 3 - Mercapto - 8 - methoxy - *as* - triazino(5,6 - b)indole.

9. 3 - Mercapto - 5 - methyl - 8 - bromo-*as* - triazino(5,6 - b)indole.

10. 3 - Mercapto - 5 - methyl - 8 - nitro-*as* - triazino(5,6 - b)indole.

11. 3 - Mercapto - 7 - methoxy - *as* - triazino(5,6 - b)indole.

12. 3 - Mercapto - 5 - propyl - 8 - chloro-*as* - triazino(5,6 - b)indole.

13. 3 - Hydrazino - 5 - methyl - *as* - triazino (5,6 - b)indole.

14. 3 - ($\beta$ - N - morpholino - ethyl)-mercapto - 5 - methyl - *as* - triazino(5,6 - b)-indole.

15. 3 - (2 - Diethylaminoethylmercapto)-5 - methyl - *as* - triazino(5,6 - b)indole.

16. 3 - (2 - Dimethylaminoethylmercapto)-5 - methyl - *as* - triazino(5,6 - b)indole.

17. 3 - Allylmercapto - 5 - methyl - *as*-triazino(5,6 - b)indole.

18. 3 - Methylmercapto - 5 - propyl - *as*-triazino(5,6 - b)indole.

19. 3 - Methylmercapto - *as* - triazino-(5,6 - b)indole.

20. 3 - Methylmercapto - 5 - methyl - *as*-triazino(5,6 - b)indole.

21. 3 - Methylmercapto - 5 - methyl - 8-chloro - *as* triazino(5,6 - b)indole.

22. 3 - Methylmercapto - 5 - methyl - 8-nitro - *as* - triazino(5,6 - b)indole.

23. 3 - Methylmercapto - 5 - propyl - 8-chloro - *as* - triazino(5,6 - b)indole.

24. 3 - Ethylmercapto - *as* - triazino - (5,6-b)indole.

25. 3 - Ethylmercapto - 5 - methyl - *as*-triazino(5,6 - b)indole.

26. 3 - ($2^1$,$4^1$ - Dinitrophenyl) - mercapto-5 - methyl - *as* - triazino(5,6 - b)indole.

27. 3 - (*p* - Nitrophenylmercapto) - 5-methyl - *as* - triazino(5,6 - b)indole.

28. 3 - Methylsulphonyl - 5 - methyl - *as*-triazino(5,6 - b)indole.

29. 3 - Ethylsulphonyl - 5 - methyl - *as*-triazino(5,6 - b)indole.

30. 3 - ($2^1$ - N - morpholinoethyl) - sulphonyl - 5 - methyl - *as* - (5,6 - b)indole.

31. 3 - Methylsulphonyl - 5 - methyl - 8-chloro - *as* - triazino(5,6 - b)indole.

32. 3 - Methylsulphonyl - 5 - methyl - 8-nitro - *as* - triazino(5,6 - b)indole.

33. 3 - (2 - Hydroxyethylamino) - 5 - methyl - *as* - triazino(5,6 - b)indole.

34. 3 - (3 - Hydroxypropylamino) - 5-methyl - *as* - triazino(5,6 - b)indole, and its hydrochloride.

75. A process for the preparation of the compounds claimed in claim 1 substantially as described with reference t any one of Examples 19 to 24.

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